

### **REMARKS**

#### **Rejection Under 35 USC § 112, second paragraph**

The Examiner has rejected Claims 80 and 94. The Examiner states that the phrase “the antibody to be detected” has insufficient antecedent basis for this limitation in the claims. The Applicants have amended the claims to read “an antibody to be detected.” In view of the amendment the Applicants respectfully request that the rejection be withdrawn.

Claims 80 and 94 have been rejected as being indefinite for the recitation of the phrase “a single epitope-containing segment.” The Applicants have amended the claims to read “one epitope-containing segment.” Support for this amendment can be found, for example, at paragraph [0021] and [0023] of the published pending application wherein a complete reading of the paragraphs demonstrates that “a single epitope-containing segment” means “one epitope-containing segment” as opposed to “two or more non-contiguous epitope-containing segments.” In view of the amendment the Applicants respectfully request that the rejection be withdrawn.

The Examiner states, “it is not clear what the Applicant means by ‘a ubiquitin fusion protein comprising a heat shock protein fused to two or more non-contiguous epitope-containing segments’.” This phrase is found only in Claim 80. The Applicants have amended the claim to read “a ~~ubiquitin~~ fusion protein comprising a heat shock protein fused to two or more non-contiguous epitope-containing segments.” Support for this amendment is found, for example, in the Summary of the Invention and in paragraphs [0012] – [0014]. In view of the amendment the Applicants respectfully request that the rejection be withdrawn.

The Examiner has rejected Claims 80 and 84 “as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.” Specifically, the Examiner states, “a broad range or limitation together with a narrow range or limitation that fails within the broad range or limitation in the same claim is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired.” Claim 80 has been amended to replace the references to “ubiquitin” with references to “heat shock protein.” Support for this amendment is found, for example, in the Summary of the Invention and in paragraphs [0012] – [0014]. In view of the amendment to Claim 80 the Applicants respectfully request that the rejection be withdrawn.

In Claim 94 Applicants cannot find where the claim “recites the broad range of heat shock protein, and then ... also recites ubiquitin ...” Thus, Applicants believe the rejection of Claim 94 was made in error and request that it be withdrawn.

Rejection Under 35 USC § 112, first paragraph

The Examiner has rejected Claims 94 – 100 for “not reasonably provid[ing] enablement for a method of reducing the levels of a predetermined protein ...” The Applicants respectfully disagree. The Examiner stated that the specification is “enabling for a method of neutralizing the biological function of a predetermined protein ...” Therefore, and solely to advance their business interests and without giving up the right to prosecute the original or similar claims in the future, have amended independent Claim 94 to recite “a method for neutralizing the biological function ~~reducing levels~~ of a predetermined protein in an animal relative to base-line levels...” Support for this amendment is found, for example, in the Summary of the Invention and in paragraphs [0022], [0024], [0036] and in Example No. 1. In view of the amendment the Applicants respectfully request that the rejection to Claim 94 be withdrawn.

Rejection Under 35 USC § 102(e)

The Examiner has rejected Claims 80 and 101 as being anticipated by Johnston, *et al.*, (US Patent no. 5,703,057), under 35 USC § 102(e). The Applicants respectfully disagree.

The Examiner states Johnston, *et al.*, teach an expression library immunization (ELI) where fragmented pathogen DNA is fused to DNA expressing mammalian genes such as ubiquitin. However, Johnston does not teach elements of the present invention as claimed. The Applicants have found that the mere use of a fusion sequence comprising one or more epitopes and ubiquitin, as taught by Johnston, *et al.*, does not result in optimal performance of the immunization of the subject animal. The Applicants have found through empirical research that “a fusion protein comprising a heat shock protein (e.g., ubiquitin), fused to an epitope or epitopes in a defined manner is useful for the stimulation of a specific immune response.” Pending application, ¶ [0012] (emphasis added). The bulk of the pending application is then directed towards the teaching and exemplification of the *defined manner* in which the fusion proteins of the present invention are made and used. For example, the present application teaches that the ubiquitin fusion proteins need to be tolerated both systemically (*i.e.*, tolerance

by the immune system) and functionally (*i.e.*, behave in a manner analogous to wild-type ubiquitin) in order to function effectively as a fusion peptide immunogen. Pending application, paragraphs [0015] - [0017]. Only insertions at particular sites in ubiquitin are “tolerated.” Pending application, paragraph [0020]. Paragraphs [0020] through [0048] then teach in detail which fusion proteins are “tolerated” and the “defined manner” in which they are made.

Rejected Claim 80 is directed towards a method of stimulating an immune response in an animal, the immune response being directed toward a fusion protein, the method comprising a) providing a DNA construct encoding a fusion protein selected from the group consisting of DNA that encodes the fusion protein of the constructions given below:

- i) a fusion protein comprising a heat shock protein fused to one epitope-containing segment, the epitope-containing segment comprising two or more identical epitopes,
- ii) a fusion protein comprising a heat shock protein fused to two or more non-contiguous epitope-containing segments, each epitope-containing segment comprising one or more identical or non-identical epitopes,
- iii) a fusion protein comprising a heat shock protein fused to one epitope-containing segment comprising two or more identical or non-identical epitopes, the epitope-containing segments being fused to the fusion sites selected from the groups consisting of the N-terminus and an internal fusion site and,
- iv) a fusion protein comprising a heat shock protein fused to one epitope-containing segment comprising one or more identical or non-identical epitopes, the epitope-containing segment being fused to the N-terminus of the heat shock protein, wherein one or more epitopes are recognized by an antibody to be detected

Johnston, *et al.*, teach none of these “defined manners” by which the fusion proteins of Claims 80 and 101 are constructed.

It is required that an anticipatory reference teaches “each and every element as set forth in the claim.” MPEP 2131. Since, Johnston, *et al.*, do not teach the defined manners in which the fusion proteins of Claims 80 and 101 are made it cannot be considered anticipatory art for the present invention. Therefore, the Applicants respectfully request that the rejection be withdrawn.

Rejection Under 35 USC § 103

The Examiner has rejected Claims 80, 94 – 97 and 99 – 101 under USC § 103(a) as being unpatentable over Johnston, *et al.*, in view of Ferro, *et al.*, and Tang, *et al.*, as evidenced by Sacca. The Applicants respectfully disagree

A finding of obviousness requires the teaching of each element of the claimed invention in the prior art. MPEP 2143. As discussed above, Johnston, *et al.*, does not teach important elements of the present invention, as claimed. The secondary references cited by the Examiner do not teach or suggest these missing elements. Therefore, the Applicants respectfully submit that the Examiner has not made a *prima facie* case of obviousness for the present invention as claimed and the rejection should be withdrawn.

Even if the prior art did teach each element of the present invention (which it does not), a finding of obviousness also requires that there must be a suggestion or motivation to combine the cited prior art references and that there must be a reasonable expectation of success. The suggestion or motivation to combine the prior art and the expectation of success must come from the prior art. It is the Examiner's burden to present "evidence" and this evidence must be "clear and particular." *In re Dembiczak*, 175 F.3d 994, 1000 (Fed. Cir. 1999). Importantly, since the Examiner is, under the law, not considered one skilled in the art, the Examiner's opinion as to what one skilled in the art may (or may not) believe is of no moment. In *in re Rijckaert*, 9 F.3d 1531, 28 U.S.P.Q. 2d 1955, 1956 (Fed. Cir. 1993). ("[T]he examiner's assumptions do not constitute the disclosure of prior art"). If the Examiner has knowledge of facts relevant to any of the pending rejections, the Examiner may file an affidavit to make those facts of record in the prosecution. The Examiner has submitted no such affidavit.

In regards to the instant rejection, the Examiner presents no such "clear and particular" evidence from the prior art and merely substitutes in its place bald-faced conclusion. For example, the Examiner states, "The motivation to use a DNA and not a protein vaccine is provided by Tang, *et al.*" Pending Office Action, page 10. Without more, the Applicants submit that this is not enough for a finding of a suggestion to combine. In fact, the MPEP cautions us "the mere fact that the references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." MPEP 2143.01, III. Even if Tang, *et al.*, (or any of the other cited references) did provide the required motivation (which they do not) they do not provide any teaching or suggestion for the

desirability of such a combination. Furthermore, the Examiner has presented no such evidence that the prior art teaches the desirability of such a combination.

Likewise, the Examiner has presented no evidence from the art teaching a reasonable expectation of success for the present claimed invention and, as above, substitutes bald-faced conclusory statements. ("One of skill in the art would have been expected to have a reasonable expectation of success because the art teaches the successful use of DNA constructs encoding for ubiquitin fusion proteins to elicit antibody responses in animals."). Pending Office Action pages 10 – 11. However, one cannot merely assume (as the Examiner does) a reasonable expectation of success before conducting the actual research and testing that resulted in the fusion proteins of the present invention.

The Applicants submit the Examiner had failed to demonstrate i) references that teach or suggest each and every element of the present claimed invention, ii) the necessary teaching and motivation founded in the prior art to combine or modify the references to obtain the present claimed invention and, iii) that there would have been an expectation of success to one of ordinary skill in the art. Therefore, the Applicants respectfully request that the pending rejection be withdrawn.

#### Rejection Under 35 USC § 103

The Examiner has rejected Claims 80, 94, 98, 100 and 101 under USC § 103(a) as being unpatentable over Johnston, *et al.*, in view of Hohfeld, *et al.*, and Tang, *et al.* The Applicants respectfully disagree.

A finding of obviousness requires the teaching of each element of the claimed invention in the prior art. MPEP 2143. As discussed above, Johnston, *et al.*, does not teach important elements of the present invention, as claimed. The secondary references cited by the Examiner do not teach or suggest these missing elements. Therefore, the Applicants respectfully submit that the Examiner has not made a *prima facie* case of obviousness for the present invention as claimed and the rejection should be withdrawn.

Furthermore, even if the prior art did teach each element of the present invention (which it does not), the Examiner has failed to provide "clear and particular" evidence that the cited prior art provided the necessary motivation to combine and the necessary reasonable

expectation of success to satisfy the requirements of a *prima facie* finding of obviousness of the pending claims and, as above, has substituted bald-faced conclusory statements.

For example, the Examiner states, "The motivation to use an anti-TNF-alpha vaccine is provided by Hohfeld who teaches the utility of immunoneutralizing TNF-alpha activity for the treatment of diseases such as multiple sclerosis and rheumatoid arthritis." Pending Office Action, page 11. Without more, the Applicants submit that this is not enough for a finding of a suggestion to combine. In fact, the MPEP cautions us "the mere fact that the references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." MPEP 2143.01, III. Even if Hohfeld (or any of the other cited references) did provide the required motivation (which they do not) they do not provide any teaching or suggestion for the desirability of such a combination. Furthermore, the Examiner has presented no such evidence that the prior art teaches the desirability of such a combination.

Likewise, the Examiner has presented no evidence from the art teaching a reasonable expectation of success for the present claimed invention and, as above, substitutes bald-faced conclusory statements. ("One of skill in the art would have been expected to have a reasonable expectation of success because the art teaches the successful use of DNA constructs encoding for ubiquitin fusion proteins to elicit antibody responses in animals."). Pending Office Action pages 12. However, one cannot merely assume (as the Examiner does) a reasonable expectation of success before conducting the actual research and testing that resulted in the fusion proteins of the present invention.

The Applicants submit the Examiner had failed to demonstrate i) references that teach or suggest each and every element of the present claimed invention, ii) the necessary teaching and motivation founded in the prior art to combine or modify the references to obtain the present claimed invention and, iii) that there would have been an expectation of success to one of ordinary skill in the art. Therefore, the Applicants respectfully request that the pending rejection be withdrawn.

Summary

In light of the above amendment, consideration of the subject patent application is respectfully requested. Any deficiency or overpayment should be charged or credited to Deposit Account No. 500282.

Respectfully submitted,



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